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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,836	07/10/2001	Domenico Valerio	3837.1US	8961

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TRASK BRITT
P.O. BOX 2550
SALT LAKE CITY, UT 84110

EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/901,836	VALERIO ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *07/01* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed October 23, 2003 has been entered. Claims 1, 8, 16, and 19 have been amended.

Applicants' election without traverse of the species Fc receptors (the immunoglobulin binding moiety), in the response filed October 23, 2003 is acknowledged. The claims will be restricted to gene delivery vehicles comprising an Fc receptor if no generic claim is finally held to be allowable.

Claims 1-20 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for delivering genetic material to a target cell, does not reasonably provide enablement for an *in vivo* method for delivering genetic material to a target cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the

claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

The following factors have been considered.

Nature of the invention. The claims are directed to a method of gene delivery via a virus-based complex. The method comprises delivering genetic material to a target cell by combining a gene delivery vehicle with a bispecific conjugate to form a gene delivery vehicle complex, and delivering the gene delivery vehicle complex to the target cell. The gene delivery vehicle comprises an expressible nucleic acid molecule comprising a recombinant gene of interest, a virus including a capsid or envelope surrounding said expressible nucleic acid molecule, and a first member of a specific binding pair, said first member of the specific binding pair expressed on an exterior of said capsid or envelope. The bispecific conjugate comprises a second member of the specific binding pair covalently coupled to a targeting moiety capable of binding to a target molecule associated with the surface of the target cell. The claims encompass *in vivo* and *in vitro* applications of the claimed method. The claims are very broad in scope with regard to the type of target cell.

The specification fails to provide an enabling disclosure for *in vivo* applications of the claimed method because the specification teaches that the only *in vivo* use for the method of gene delivery is for gene therapy (p. 1, lines 1-23). No other use for the method of *in vivo* gene delivery is contemplated in the specification. However, the specification does not adequately teach how to use the method of gene delivery in gene therapy applications. The specification fails to teach any method for transferring any gene into a target cell and expressing that gene at a therapeutic level.

Amount of direction or guidance presented and the presence or absence of working examples. The specification fails to provide an enabling disclosure for *in vivo* gene delivery because the guidance provided does not adequately teach how to make a gene delivery complex of the type claimed and use it to achieve targeted delivery of a nucleic acid to an *in vivo* target cell. The claims encompass

methods of *in vivo* gene delivery. However, the limited guidance and limited working examples provided in the specification do not adequately teach one skilled in the art how to make and use the claimed compositions for *in vivo* gene delivery. The working examples demonstrate that biotinylated G-CSF specifically binds to its native receptor expressed on the membrane of a mammalian cell line. Example 3 demonstrates that hFcgRIa expressed on the surface of retrovirus packaging cells (PAFcR cell line) specifically binds mouse IgG2a. Example 5 demonstrates that the fusion proteins FcRenv-15 and FcRenv-70 (a fusion of the hFcgRIa receptor and a MoMuLV envelope protein) specifically bind IgG2a. The fusion proteins tested were free in solution rather than part of a virus particle. The working examples do not demonstrate how to make a targeting complex of the type claimed. Furthermore, the working examples do not teach how to use the claimed targeting complex for targeted delivery of a nucleic acid to a target cell. In the absence of specific guidance, one skilled in the art would have been required to engage in undue experimentation to use the claimed methods for *in vivo* gene delivery.

The specification does not provide working examples of *in vivo* gene delivery.

The specification fails to provide an enabling disclosure for appropriate targeting moieties because the guidance provided in the specification does not adequately teach targeting moieties that can be used in complexes of the type claimed to successfully achieve targeted gene delivery. The specification teaches that immunoglobulins can be used to target desired cell surface antigens (p. 13, lines 32-36) or that ligands can be used to target cell surface receptors (p. 14, lines 1-4). However, the specification does not teach how to identify appropriate target molecules that will bind to the targeting complex so that the complex is efficiently internalized. The specification states that "not every target cell-specific molecule might serve as an internalization site for viruses bound to it" (p. 20, lines 10-11). However, the specification does not teach targeting moieties that can be used to construct complexes that will deliver nucleic acid to a target cell so that the exogenous nucleic acid is expressed by the target cell. The working examples do not demonstrate uptake and expression of the exogenous nucleic acid to a

desired target cell. In the absence of an appropriate targeting moiety, one skilled in the art would be required to engage in undue experimentation to achieve targeted gene delivery to the wide variety of target cells encompassed by the claims.

State of the prior art and predictability of the art. The claims encompass methods of gene therapy. However, gene therapy is not routinely successful. Therefore, the disclosure must enable the full scope of the claimed methods with specific guidance. However, the specification does not provide any guidance as to the level of gene expression required, the number of transduced cells needed, the type of cells that need to be transduced, where or when the gene should be expressed, or the frequency of administration of the gene therapy vector required, for treatment of any pathological condition. Furthermore, the claims do not require expression of the introduced nucleic acid molecule, but the disclosure indicates that expression is essential to the invention. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). Thus, absent any showing that the claimed methods are capable of producing the intended therapeutic effect in

gene therapy applications, the claims directed to methods for *in vivo* gene delivery are not enabled by the disclosure.

In the absence of specific guidance, one skilled in the art would not know how to apply the general teachings provided in the specification to make a gene delivery complex capable of providing targeted gene delivery to a specific cell type. As discussed above, methods of targeted gene delivery are unpredictable because the technology for getting appropriate expression in the target cell to achieve the desired effect is not routine.

Given the limited working examples, the limited guidance in the specification, the broad scope of the claims, and the unpredictability of applying the contemplated gene delivery methods to gene therapy, undue experimentation would have been required for one skilled in the art to practice the claimed gene delivery method *in vivo*.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the expression of the delivered nucleic acid in the target cell.

Claims 2, 7, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite in its recitation of "wherein said first member of the specific binding pair is configured without a specific affinity for said target molecule" because the claim language is confusing.

Claim 7 is indefinite in its recitation of "wherein said capsid or envelope is configured to be incapable of binding to the target cell" because it is unclear if the capsid or envelope is actually incapable of binding to the target cell.

Claim 14 is indefinite in its recitation of "derived from" because the nature and number of derivative processes are not specified. Thus, the metes and bounds of the virus recited in the claims is not clearly set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Curiel et al. (1994).

The claims are directed to a method of gene delivery via a virus-based complex, a gene delivery vehicle, and a kit of parts. The gene delivery vehicle comprises a virus having a capsid or envelope, an expressible nucleic acid molecule comprising a recombinant gene of interest enveloped by said capsid or envelope, and a first member of a specific binding pair recombinantly expressed on an exterior surface area of said capsid or envelope. The kit of parts comprises the gene delivery vehicle and a bispecific conjugate. Various kits containing various forms of the gene delivery vehicle and bispecific conjugate are claimed.

Curiel et al. (1994) disclose a gene delivery vehicle comprising a biotinylated adenovirus. Plasmid DNA encoding β-galactosidase is coupled to the exterior of the viral particles by streptavidin-polylysine complexes. Thus, the biotinylated adenovirus coupled to the plasmid DNA via the steptavidin-polylysine complex is the gene delivery vehicle as defined in Claim 1. Curiel et al. further disclose a

conjugate for the gene delivery vehicle consisting of polylysine coupled to a human immunoglobulin or a goat anti-human immunoglobulin which has affinity for a molecule associated with the surface of the target cell (p. 578, column 1, paragraph 2). The conjugate binds to the DNA of the gene delivery vehicle through the polylysine portion of the conjugate and binds to the the surface of the target cell via the human Ig or anti-human Ig portion of the conjugate. When the conjugate comprises human Ig it binds to Fc receptors on the surface of the target cell, a human B-cell. When the conjugate comprises anti-human Ig it binds to surface Ig on the B-cell target. *In vitro* experiments demonstrated that when Ig-polylysine or anti-Ig-polylysine conjugates were used to form the gene delivery complex reporter gene expression increased up to three-fold more than when transferrin-polylysine or polylysine was used in the formation of the complex. *In vivo* experiments demonstrated that SCID mice injected intraperitoneally with an adenovirus/polylysine/pCMVβgal construct expressed β-gal in 22% of CD19+ peritoneal cells 3 days after injection (p. 582). The gene delivery complex administered to the SCID mice was not specifically targeted to B-cells.

The kits of Claims 8-15 are inherently disclosed by Curiel et al. (1994).

Thus, the claimed invention is disclosed in the prior art.

Claims 1-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Roux et al. (1989).

The claims are directed to a method of gene delivery via a virus-based complex, a gene delivery vehicle, and a kit of parts. The gene delivery vehicle comprises a virus having a capsid or envelope, an expressible nucleic acid molecule comprising a recombinant gene of interest enveloped by said capsid or envelope, and a first member of a specific binding pair recombinantly expressed on an exterior surface area of said capsid or envelope. The kit of parts comprises the gene delivery vehicle and a bispecific conjugate. Various kits containing various forms of the gene delivery vehicle and bispecific conjugate are claimed.

Roux et al. (1989) disclose a retroviral targeting vector aimed at major histocompatibility complex (MHC) class I or class II antigens that will infect human cells. The vector comprises a recombinant mouse ecotropic murine leukemia virus coated with biotinylated antibodies directed against the viral envelope protein gp70. Biotinylated antibodies directed against MHC class I antigens are associated with the target cell. Biotinylated antibodies against the viral envelope protein on one side, and against the specific cell membrane marker on the other side, were bridged by streptavidin and used to link the virus to the host (Abstract). Virus bound to MHC class I antigens are efficiently internalized by endocytosis in numerous cell types (p. 9079, column 2, paragraph 1). The virus-containing complexes were successfully used to infect human cells with ecotropic murine retroviruses by means of MHC class I and class II antigens (Abstract). Roux et al. thus disclose the gene delivery vehicle of the invention, wherein the gene delivery vehicle comprises the recombinant murine retrovirus and the gp70-specific biotinylated antibody bound to streptavidin. The biotinylated antibody directed against the MHC class I antigen corresponds to the conjugate as defined in the instant invention. The retrovirus-containing gene delivery vehicle of Roux et al. binds to the biotinylated anti-MHC class I antibody via a streptavidin-biotin linkage. Thus the claimed compositions and methods are disclosed by Roux et al. (1989).

The kits of Claims 8-15 are inherently disclosed by Roux et al. (1989).

Thus, the claimed invention is disclosed in the prior art.

Claims 1-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Russell et al. (1993).

The claims are directed to a method of gene delivery via a virus-based complex, a gene delivery vehicle, and a kit of parts. The gene delivery vehicle comprises a virus having a capsid or envelope, an expressible nucleic acid molecule comprising a recombinant gene of interest enveloped by said capsid or envelope, and a first member of a specific binding pair recombinantly expressed on an exterior surface area of said capsid or envelope. The kit of parts comprises the gene delivery vehicle and a bispecific

conjugate. Various kits containing various forms of the gene delivery vehicle and bispecific conjugate are claimed.

Russell et al. (1993) disclose a retrovirus displaying a functional antibody fragment that binds to a hapten. The gene encoding the antibody fragment was fused to the gene encoding the viral envelope protein ($Pr80^{env}$) of the ecotropic Moloney murine leukemia virus (MoMLV) to produce retroviral particles with specific hapten binding activity (Abstract). The hapten-binding particles were able to transfer the *neo* gene and the antibody-envelope fusion gene to mouse fibroblasts. Russell et al. report that the display of antibody fragments on the surface of recombinant retroviral particles can be used to target virus to cells for gene delivery.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (571) 272-0548.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER